of tumor cells which are cuboidal rather than columnar at the periphery. Some of the sections show particles of bone in the stroma. Section from the block cut sagittally through a tooth shows a normal tooth outside the tumor.

MICROSCOPIC DIAGNOSIS. Adamantinoma.

In conclusion, I wish to express thanks to Professor F. B. Mallory for critically reviewing this article and the sections; to Mr. L. S. Brown, of the Massachusetts General Hospital Laboratory for his kindness in making the photomicrographs, and to Mr. Walter McCrocklin, a student in our laboratory, for the sketch drawn from the museum preparation of half the gross specimen and from the description in the laboratory records.

NOTE.—Since this article was written the boy reported five months after operation and showed no sign of recurrence.

THE PATHOLOGICAL AND CLINICAL ASPECTS OF THROMBO-ANGIITIS OBLITERANS.[1]

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IT is not my purpose to burden you with an extensive and detailed account of the pathological and clinical aspects of the disease thrombo-angiitis obliterans, because the clinical picture and the main facts regarding the pathological lesions are certainly sufficiently known to you. I shall attempt, rather, to present the subject matter from the view-point of one who has been fortunate enough to have had a large amount of clinical material at his disposal (more than 300 cases), from which all phases of the pathology and clinical course could be investigated.

Perhaps the best general view of the morbid process, the most thorough understanding and most satisfactory conception can be had by a general comparative consideration of the pathological lesions and their corresponding clinical manifestations.

If I were asked to formulate a general concept of thrombo-angiitis obliterans I should answer as follows: Imagine a patient seeking relief for acutely swollen superficial veins of the lower or upper extremities, of sudden advent, and with all the manifestations of an acute thrombophlebitis. Imagine this process involving a considerable portion of the distal territory of the internal saphenous vein, followed by abatement of symptoms, and consequent resolution or healing. You will be in no doubt as to the general pathology nor as to the clinical course of the condition,

[1] Read before the College of Physicians of Philadelphia.

though your estimation of the etiology will in most instances, at least, be obscure.

Transfer this picture to the deeper vascular system, over the distribution of the external and internal plantar arteries and veins, the dorsalis pedis, anterior tibial, posterior tibial, and the peroneal arteries and veins, that is, with lesions in territories where objective manifestations are absent—and you will be depicting to yourselves, what corresponds to my own conception of the pathological process in the disease, thrombo-angiitis obliterans. So here, too, we postulate an acute inflammatory and thrombotic lesion, but one involving deep arteries or veins, or both, as the initial stage of the pathological anatomy.

Whereas the patient afflicted with an inflammatory and thrombotic lesion of the superficial veins presents objective signs easy of recognition, the patient suffering from thrombo-angiitis obliterans in its earlier stages may offer no objective evidences suggestive of the true nature, or of the site of the lesion. It was but in a very few cases of my own series (more than 300) that I felt justified in ascribing certain symptoms to the incipient stage of the disease. Severe, non-localizable shooting pains in the calf or foot, attended with difficulty in walking, or, possibly, with tender calf muscles, with or without vasomotor symptoms and coldness in the foot, with or without obliteration of the dorsalis pedis and posterior tibial pulses, may be the only symptoms. It is only when we compare the history with the future clinical course and pathology that we can relegate such indefinite signs to the onset of the affection. In most instances, however, the patient will not seek advice for such initial symptoms, either because they are not sufficiently severe to require the attention of a physician, or because they are incorrectly regarded as rheumatic in origin, possibly due to trauma, cold, the presence of flat or weak foot, or because they are explained on the basis of some other minor ailment.

Strange to say, patients afflicted with thrombo-angiitis obliterans may present symptoms which differ in no way from those attending the thrombophlebitis of the superficial veins, or so-called migrating phlebitis. These are the cases of thrombo-angiitis obliterans in which an acute inflammatory thrombosis involves smaller or larger portions of the external or internal saphenous vein, radial, ulnar, median cephalic or median basilic vein. Such cases are the most instructive of all, for they are the ones which afford us material for pathological study. Here the veins are accessible; portions can be surgically removed when the lesions are in the acute inflammatory stage and submitted to histological examination.

While the former type of case is difficult to diagnose the variety with concomitant migrating phlebitis can be recognized by a

study of the vein lesions under the microscope. If the tissue be examined when the lesions are still in the early inflammatory stage, before organization or healing has taken place, certain characteristic and specific lesions can be identified, changes which I have elsewhere described as pathognomonic for thrombo-angiitis obliterans.

Having learned that the incipient lesion of thrombo-angiitis obliterans is an acute inflammatory one, involving the arterial and venous walls, we will expect an occlusive thrombosis as the immediate sequence, and will not be surprised to learn that this stage gradually gives way to one of organization and canalization, resulting in a healed product in which the vessel becomes converted into a cord, more or less adherent to its surroundings, in which even the neighboring nerves may become agglutinated and enveloped in fibrotic vascular cord.

It is the interference with the circulatory conditions of the limbs brought about by the extensive occlusive process that is responsible for most of the clinical manifestations of thrombo-angiitis obliterans. So that it may be safely said that patients afflicted with thrombo-angiitis obliterans do not suffer directly from the disease itself but from the disastrous occlusive thrombosis which signalizes Nature's method of healing a vascular lesion, that has long since disappeared.

From a study of the pathological material, and from a comparison of the lesion with the clinical history, we must conclude that insidious or clinically unrecognizable exacerbations of the lesion may occur from time to time, so that the involvement of the vascular territory with the obliterative lesion is a progressive one until the summit of the organized clot reaches the popliteal, in rare cases the femoral or even the iliac. It will not occasion astonishment, therefore, that the clinical manifestations, too, become more and more serious as time goes on.

Nor must we be surprised if thrombo-angiitis obliterans simulates clinical complexes brought about by arterial occlusion from other causes. Differentiation from arteriosclerotic gangrene, intermittent claudication due to arteriosclerosis, endarteritic occlusion, and other thrombotic conditions may at times be difficult. It is the fact that thrombo-angiitis obliterans occurs in *very young individuals* in whom both the *vis a tergo* and the cardiac power are adequate for compensation, and in whom the vascular adaptability is elastic in its scope—it is this fact that accounts for the seemingly almost inexplicable circumstance, that gangrene occurs *so* late, or may be absent, in spite of vast and extensive obliteration of arteries and veins. It is to the development of the collateral circulation, therefore, that we owe, in part at least, the production of a very peculiar, striking, and characteristic clinical picture, recognizable even though mani-

festations of the acute stage of the disease, or manifestations, such as migrating phlebitis, are absent.

CLINICAL SYMPTOMS. I will not go into detail concerning the clinical symptoms, for they are sufficiently well known. It may be interesting merely to make brief mention of my own routine method of physical examination, one that has stood me in good stead, in the recognition and also in the differentiation of this disease from those other that closely simulate it, and then to illustrate by lantern slides the chief feature of the pathology of the disease.[2]

My own scheme includes the investigation of the following points: (1) the general appearance of the limb in the horizontal position; (2) in the pendent position; (3) the presence or absence of ischemia in the elevated position; (4) the estimation of the *angle of circulatory sufficiency*; (5) pulsation in the palpable vessels, iliac, femoral, popliteal, posterior tibial, anterior tibial, and dorsalis pedis in the case of the lower extremities, radial, ulnar, brachial, and axillary in the upper extremities; (6) the occurrence of *induced, reactionary rubor* or *erythromelia*.

1. THE GENERAL APPEARANCE OF THE LIMB. Any departure from the normal should be noticed. The presence of fissures, ulcers, perforating ulcers, bullæ, ecchymoses, impaired nail growth, gangrenous areas, signs of infection or lymphangitis or venous thrombosis, evidences of malnutrition, such as atrophy, exceptional prominence of the bony landmarks and extensor tendons, conservation or effacement of the normal irregularities of contour through edema or through thickening of the skin and subcutaneous tissues, are features of importance. Variations from the normal color—particularly marked pallor in the horizontal position, a play of color over the foot, even in the horizontal position; cyanosis, increased redness—all these are manifestations of either impaired circulation or vasomotor disturbance.

2. IN THE PENDENT POSITION. With the foot in the pendent position and in the absence of inflammation a red flush involving the toes and dorsum, as well as the sole of the foot, extending upward for a variable distance, rarely farther than the ankle, is a phenomenon that is characteristic of many cases and many types of reduced circulation due to vascular obturation. This is a condition of *rubor* or *erythromelia* (Gr. *erythros* = red, *melia* = limb). It is brought about by a compensatory dilatation of the superficial capillaries, and is most characteristic of the disease, thrombo-angiitis obliterans, although also found in other arterial affections attended with closure of larger vessels. It is frequently present in

[2] The lantern slides are not reproduced in this paper; some have been published in previous papers on thrombo-angiitis obliterans.

arteriosclerotic and diabetic cases as well. It seems to be an effort on the part of Nature to make up for the impairment of circulation by virtue of dilatation and engorgement of the superficial capillaries. Although more striking in the pendent position the rubor may also be present in the horizontal position, and when continuously in evidence may be termed *chronic rubor* and *chronic erythromelia* in contradistinction to the *reactionary rubor* that may be induced by depressing the limb after previous elevation.

3. Ischemia or Blanching. This usually sets in rapidly when the affected limb is elevated whenever mechanical interference with the circulation is present. The extent of blanching and the rapidity with which it appears are both valuable aids in the estimation of the amount of obstructive arterial disease. When the affected limb is cold the tips of the toes may remain slightly blue or cyanotic. Should the blanching be slow in appearing, or very hard to determine, pressure upon the tips of the toes after the limb has been elevated for some time will demonstrate whether the part has become depleted of blood or not ("expression test"). Compression of the toes of the elevated foot in normal cases will reveal the presence of sufficient bright arterial blood (rarely slightly cyanotic), while a varying degree of ischemia, with or without marked cyanosis, will accompany obliterated or obstructed arteries.

4. The Angle of Circulatory Sufficiency. The estimation of this angle is based on the supposition that the normal limb, when elevated so as to be perpendicular to the horizontal plane, that is 180 degrees, still retains most of its color. When the circulatory mechanism is defective, and the limb is elevated to the vertical, a variable degree of blanching of the foot occurs. If the leg is then gradually depressed *the angle at which a reddish hue returns* (angle of circulatory sufficiency) will be found to vary considerably. In some cases it will be necessary to depress the limb to the horizontal before evidences of return circulation are manifest. The angle of circulatory sufficiency would then be 90 degrees. In many cases of arterial disease the estimation of this angle is a valuable adjuvant not only in the recognition of the extent of the circulatory disturbance but also in prognosis.

5. Absence of Pulsation as an Indication of Arterial Occlusion. We should be able to feel the femoral, posterior tibial, popliteal, and dorsalis pedis arteries pulsating in almost all individuals who possess patent arteries. In rare cases the dorsalis pedis may be aberrant in its course and therefore not palpable, or neither the dorsalis pedis nor popliteal may be accessible to the touch because of the stoutness of the patient.

To palpate the popliteal satisfactorily the patient is placed on his abdomen, lying prone. The leg is held at right angle, that is, vertical, the patient being asked to relax the hamstring muscles.

The artery is then sought in the upper half of the popliteal space, just outside of the semimembranosus and semitendinosus tendons, the fingers being pressed downward against the femur. In the upper extremities, the radial, ulnar, and brachial and axillary arteries should be examined for pulsation.

The absence of pulsation is, as a rule, an indication of occlusion at the point palpated, although in rare instances postmortem dissections have shown that the site of obliteration is somewhat higher up.

6. Reactionary Hyperemia, Rubor, or Reactionary Erythromelia. By this term we mean an *induced rubor* that manifests itself in the pendent position of the foot after the limb has been previously elevated to the vertical. It is a physiological phenomenon that ischemia, or blanching of a limb artificially produced by an Esmarch or Martin bandage, will be followed by sudden dilatation of the capillaries of the peripheral parts when the circulation is allowed to return. So, also, blanching will occur in a leg whose larger arteries are occluded on mere elevation 60 to 90 degrees above the horizontal without the use of any artificial means. When such a blanched limb is then depressed to the pendent position a similar induced or reactionary rubor will become manifest. This well-known manifestation may be invoked in the examination of cases in which impaired circulation due to arterial occlusion is suspected. It will be found particularly useful in cases of thrombo-angiitis obliterans, although also demonstrable in other cases of organic vascular disease. In early cases it is especially valuable, for it may be present long before the chronic condition of *rubor* or *erythromelia* develops.

With this introduction I may be permitted to give a brief survey of the pathology of the disease, pointing out the histological lesions characteristic of the various stages of thrombo-angiitis obliterans, and also calling attention to the facts that point to the inflammatory nature of the disease and to those observations that suggest that we are dealing with a process of microbial etiology.

In 1908 I pointed out that the name endarteritis obliterans as applied to thrombo-angiitis obliterans should be discarded, since the occlusive lesion is a thrombotic one, affecting arteries as well as veins of the extremities, and that it is independent of atherosclerosis or arteriosclerosis.

My investigations, which included a thorough pathological and histological study of the vessels in 45 amputated lower extremities, 1 upper extremity, and 25 pieces of superficial veins resected and exsected from the lower and upper extremities during attacks of so-called migrating phlebitis, have demonstrated that when the patient comes to the physician for observation the larger arteries, and often the larger veins, are completely obliterated.

As a rule the plantar vessels, dorsalis pedis and many of its branches, anterior tibial, posterior tibial, peroneal and sometimes the popliteal are already completely closed, although any one or more of these vessels may escape. One or both the venæ comites may partake of the same lesion. The obturating tissue is for the most part representative of or indicative of a healed lesion, or the end-stage of a process whose incipiency is marked by an acute inflammation of the vessel wall, with consecutive, red, occlusive thrombosis of the affected vessel. It is only in rare instances that the early stages of the vascular lesion are found in the deep vessels, but in superficial veins when they are affected with the lesion of migrating or thrombophlebitis, the early or acute stage of the disease can be studied.

Gross Pathology. The deep vessels of the amputated legs regularly show an extensive obliteration of the larger arteries and veins. Besides this there are two other lesions which vary greatly in their intensity, namely, the peri-arteritis and the arterio-sclerosis. The appearance of the vessels on gross section depends upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessels, and that appears to be pierced at one or a number of points by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency and does not at all resemble the crescentic or semilunar occluding masses typical of arteriosclerosis. The vessel itself is usually contracted, so that its wall appears somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old obliterating process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel from the dorsalis hallucis into the popliteal.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue. Frequently it becomes softer, more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the brownish tissue gives way to soft, reddish masses which are evidently the results of recent thrombosis. In some cases this thrombotic process occupies large portions of the vessel's course; in others it is of short extent and terminates in a long cone of recent thrombus.

The veins share equally with the arteries in the lesion of occlusion. In some cases the veins are more extensively involved than the arteries, and this is particularly true of the collaterals of the posterior tibial, which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or of the whole of the anterior tibial; occlu-

sion of the dorsalis pedis, and dorsalis hallucis, of the posterior tibial and plantar vessels, with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely a large portion of the dorsalis pedis is open, with the beginning of the occlusion in the upper part of this vessel or in the lower part of the anterior tibial.

Besides the lesion of occlusion there are two other striking changes, namely, a certain amount of arteriosclerotic thickening and peri-arteritis. Arteriosclerosis is absent in the younger cases; when present it is never pronounced except in those rare instances in which the patient has suffered from the disease for many years, and has reached the age of forty or more. As a rule, we note but a very slight degree of whitening or thickening of the intima, here and there, in the patent portions of the vessels. In a very few cases small atheromatous patches are present.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels. Wherever the vessels are occluded there is apt to be an agglutinative process which binds together the artery and its collateral veins, and sometimes also the accompanying nerve, so that liberation of the individual vessels by dissection is difficult. The adhesive condition is due to fibrous tissue growth and varies considerably in its amount. The peri-arterial fibrosis varies, sometimes being almost absent, at other times so great that isolation of the vessels or nerves becomes impossible and the vascular structures make up one dense rigid cord.

Histopathology. The lesions may be considered in two stages: (1) the healed or organized stage, and (2) the acute or incipient stage of thrombosis. Between the earliest alterations in the deep arteries and veins and superficial veins and the finished product there are a large number of intermediate pictures that illustrate the metamorphosis of the obturating clot into the intravascular cicatrix.

1. *Healed or Organized Stage.* The most common lesion is a total obliteration of the lumina of arteries and veins by connective tissue. Histologically this may be extremely varied in the general appearance, but each picture can be interpreted correctly as having its origin in the lesion of occlusive thrombosis. This obturating connective tissue usually harbors numerous small vessels, pigment containing hemosiderin, and a fair amount of connective-tissue cells. The canalizing vessels when they become dilated form smaller or larger sinuses, giving the fenestrated or cribriform lesion seen on microscopic section of the vessels, or when the canalizing vessel becomes eccentrically placed, and sufficiently large, this sinus is responsible for the appearances which have been incorrectly interpreted as the product of an endarteritis obliterans.

Elastic-tissue stains demonstrate characteristic differences between this process and arteriosclerosis. Thus the region of the organized clot is almost completely free from elastic tissue. The small amount which is present is concentrically disposed about the new-formed vessels.

Still more suggestive and instructive is the finding of various stages of the disease in different members of the same vessel sheath. Thus in one of the lantern slides shown a large artery affords a view of the old lesion as well as one of its venæ comites. Another accompanying vein, however, is in the "acute" stage of the disease, a smaller venule or satellite being in the intermediary stage, where certain "miliary giant-cell foci" make their appearance. Such pictures not only reveal the thrombotic nature of the disease, but also present an argument in favor of the following two assumptions: that the disease begins with an inflammatory lesion attended with occlusive thrombosis, and that it affects the arteries and veins in a sort of relapsing fashion, very much in the same manner as in the veins in migrating phlebitis.

The termination of the occluding tissue in arteries and veins is often seen in the form of a rounded, convex projection looking upward (cephalad) and lying in practically healthy vessel wall. At other times the old occluding tissue is capped by an additional clot which rises in pyramidal fashion ending by a long capering extremity.

2. *The Acute or Specific Lesion.* The early lesions are so characteristic histologically that their appearances are practically specific for thrombo-angiitis obliterans and may permit the pathologist to make a diagnosis of the disease. They are rarely to be seen in the deep vessels for the reason that patients do not allow amputation until the disease has lasted for months or years. However, they can be well studied when these are the seat of the typical migrating phlebitis, and have been shown by me to be identical with the acute lesions in the deep vessels.

The earliest changes appear to be the usual evidences of an acute inflammatory process involving all the coats of the vessel. The media, adventitia, and perivascular tissues are infiltrated with polynuclear leukocytes and the lumen of the vessel is completely filled with red clot. In the peripheral portions of the clot, larger or smaller foci of leukocytes (purulent foci) begin to form, whose growth occurs by virtue of immigration of leukocytes. Then certain peculiar giant-cell foci develop and are characteristic. They contain giant cells, endothelioid cells or angioblasts and numerous broken-down leukocytes. These foci then undergo connective-tissue replacement. The giant cells gradually disappear; numerous small vessels are formed, the final product being a fibrous nodule containing vessels and some pigment. In the rest of the occluding clot the organizing process is somewhat different, resembling

that which characterizes the organization of blood clot in other thromboses.

In short, the lesions in thrombo-angiitis obliterans are in chronological order: (1) an acute inflammatory lesion with occlusive thrombosis, the formation of miliary giant-cell foci; (2) the stage of organization or healing, with the disappearance of the miliary giant-cell foci, the organization and canalization of the clot, the disappearance of the inflammatory products; (3) the development of fibrotic tissue in the adventitia that binds together the artery, vein, and nerves.

A CONSIDERATION OF THE TREATMENT OF PERIPHERAL GANGRENE DUE TO THROMBO-ANGIITIS OBLITERANS, WITH REFERENCE TO FEMORAL VEIN LIGATION AND SODIUM CITRATE INJECTIONS.[1]

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The surgical treatment of impending or actual gangrene of the extremities due to pathological changes in the peripheral blood-vessels, termed thrombo-angiitis obliterans by Buerger, embraces a number of procedures which attempt to increase the circulation in the impaired limb. The successful application of a surgical principle to cure a pathological process presupposes the possibility of either totally extirpating the diseased area or structure, or the correction of a departure in normal organic function until such time as may be required for tissue restoration or regeneration to take place.

Buerger's convincing demonstration of the true pathological entity of the disease which bears his name leaves no doubt as to the presence of the extensive bloodvessel changes which have already taken place when these cases are first observed. In most instances the disease has progressed to the point of impending gangrene or actual digital death, and all surgical measures for relieving the great suffering and distress of these patients are really only palliative in nature.

A considerable amount of experimental laboratory work, performed abroad and in this country, for the purpose of establishing the value of arteriovenous anastomosis in the treatment of this disease, has proved rather conclusively that true reversal of the circulation in the affected limb cannot be accomplished, even though Carrell and Guthrie successfully established in their labora-

[1] Read before the College of Physicians of Philadelphia.